Middle cerebral artery-peak systolic velocity in dizygotic twins with anti-E alloimmunization

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Abstract

Middle cerebral artery-peak systolic velocity (MCA-PSV) has been reported to predict fetal anemia with similar accuracy as amniotic ΔOD_{450} assay. Alloimmunized dizygotic twin pregnancy allows us to compare anemic and non-anemic twins in the same intrauterine environment. We herein present a case of Rh (E)-incompatible dizygotic twin pregnancy, where MCA-PSV could precisely detect the anemia in one of the twins. A 36-year-old woman, whose previous child required exchange transfusion due to hemolytic anemia of newborn (HFDN), conceived twins after in vitro fertilization-embryo transfer. At 24 weeks' gestation, MCA-PSV of twin A and twin B were 23.9 cm/s (0.8 multiples of median: MoM) and 30.7 cm/s (1.0 MoM), respectively. At 31 weeks' gestation, MCA-PSV values of both twins were sharply elevated to nearly 1.4 MoM. Thereafter, MCA-PSV of twin A fell to 1.0 MoM, whereas MCA-PSV of twin B exceeded 1.5 MoM at 34 weeks' gestation. Development of fetal anemia was suspected and emergency cesarean section was performed. Twin B that showed moderate anemia with positive direct Coombs' test was diagnosed as HFDN due to anti-E alloimmunization. Twin B required phototherapy and red cell transfusion, but exchange transfusion was safely obviated.

Keywords; alloimmunization, amniocentesis, Doppler, hemolytic disease of newborn

Introduction

The first step of the management of alloimmunized pregnancies is serial measurement of maternal irregular antibody titers. Once the titer elevates beyond critical level (usually >1:32), paternal evaluation should be indicated [1]. If the patient's partner is negative for the particular red cell antigen, then the further evaluation of the fetus is unnecessary. If paternal blood type is positive for the antigen, the next step usually necessitates fetal evaluation for possible anemia. The main approach for the prediction of fetal anemia has been amniocentesis to measure bilirubin concentration in the amniotic fluid through ΔOD_{450} assay.

In 2000, Mari et al. reported that Doppler measurement of fetal middle cerebral artery peak systolic velocity (MCA-PSV) is highly predictive for fetal anemia caused by red cell alloimmunization [2]. They found that MCA-PSV of >1.5 multiples of median (MoM) corresponds to moderate to severe fetal anemia. Elevated MCA-PSV seen in fetal anemia is likely to result from increased cardiac output and decreased blood viscosity. Although theoretically velocities of all fetal vessels should be increased, the MCA is suitable for the quantification because its position frequently permits a low angle of insonation. Afterwards, many investigators verified the usefulness of MCA-PSV [3-5] and increasing number of obstetricians come to believe that MCA-PSV measurement could safely replace invasive amniocentesis in the management of alloimmunized pregnancies.

For women who previously delivered neonate with hemolytic anemia, the maternal antibody titer does not necessarily reflect the risk for the development of fetal anemia. As a result, repetitive amniocentesis used to be the only option to monitor such fetuses [1]. Amniocentesis is more difficult and requires more skilled technique in multiple pregnancies than in singleton pregnancies. In this respect, introduction of MCA-PSV could be of particular benefit in multiple pregnancies of women who previously delivered the affected neonate. Recently, Dashe et al. reported that MCA-PSV values in uncomplicated twins are comparable to published singleton norms [6]. Nevertheless there have been only few case reports where measurement of MCA-PSV is actually applied to alloimmunized twin pregnancies [7].

Here, we report a case of Rh (E)-incompatible dizygotic twin pregnancy where sequential monitoring MCA-PSV could precisely predict fetal anemia in one of the

1 twins.

Case Report

A 36-year-old woman (gravida 2, prara 2) conceived dizygotic twins following in vitro fertilization-embryo transfer. Her first pregnancy ended in intrauterine fetal demise at 39 weeks' gestation for unknown cause. During her second pregnancy, her serum anti-E antibody titer arose from 1:8 (32 weeks' gestation) to 1:64 (36 weeks' gestation) and a mature female baby was vaginally born at 38 weeks' gestation. The baby showed moderate anemia (hemoglobin=9.2 g/dl) with hyperbilirubinemia (total bilirubin=4.9 mg/dl) at birth, leading to diagnosis of hemolytic anemia of newborn (HFDN). Total bilirubin arose to 11.9 mg/dl after 12 hours and exchange transfusion was instituted.

The blood type of the patient was Rh (CCDee) and that of the spouse was Rh (CcDEe). Thus, theoretically Rh (E)- or Rh (c)-incompatibility could exist between the mother and the twins. For a woman whose previous child was affected, maternal antibody titer does not necessarily reflect fetal anemia [1]. Therefore, we monitored MCA-PSV for each twin. At 24 weeks' gestation, maternal anti-E titer was 1:16 and anti-c was undetectable. MCA-PSV of twin A and twin B were 23.9 cm/s (0.8 MoM) and 30.7 cm/s (1.0 MoM), respectively. Maternal anti-E titer fluctuated between 1:8 and 1:32 with highest titer observed at 26 weeks' gestation. Anti-c titer remained undetectable throughout the pregnancy. Serial changes in MCA-PSV of twin A and B are shown in Figure 1. At 31 weeks' gestation, MCA-PSV values of both twins were sharply elevated to nearly 1.4 MoM. Betamethasone was administered to the mother for prevention of neonatal respiratory distress syndrome. MCA-PSV of twin A fell to 1.0 MoM thereafter, whereas increased MCA-PSV (≒1.4MoM) of twin B persisted and exceeded 1.5 MoM, which corresponds to moderate anemia, at 34 weeks' gestation. Considering the gestational age, instead of verifying fetal anemia with invasive amniocentesis or cordocentesis, emergency cesarean section was selected.

Twin A was a female baby weighing 1644 g and had Apgar scores of 8 at 1 minute and 9 at 5 minutes with umbilical artery pH of 7.359. Twin B was a male baby weighing 2070 g and had Apgar scores of 8 at 1 minute and 10 at 5 minutes with umbilical artery pH of 7.337. Umbilical venous blood showed hemoglobin of 12.9 g/dl (normal) for twin A and 7.6 g/dl (moderate anemia) for twin B. Rh type of twin A and B proved to be CCDee (same as the mother) and CcDEe (same as the father),

respectively. Amniotic sample was collected from each twin at the time of cesarean section. ΔOD_{450} values plotted on Liley's chart showed that twin A was within zone 1 (no anemia) and twin B was within zone 2 (moderate anemia) [8].

Initial laboratory data from twin A and B were shown in Table 1. Twin B with positive direct Coombs' test and moderate hyperbilirubinemia was diagnosed as HFDN due to Rh (E) incompatibility. Postnatal course of twin A was uneventful. Twin B required phototherapy and red cell transfusion, but exchange transfusion was safely obviated.

Discussion

It is known that maternal antibody titer does not necessarily reflect fetal anemia for women who previously delivered neonate with hemolytic disease [1]. In fact, maternal anti-E titer fluctuated but never exceeded the critical level (1:32). In such cases, repetitive amniocentesis used to be the only way to predict fetal anemia. Amniotic sample collected at the time of cesarean section showed that ΔOD_{450} value of twin A was within zone 1 (normal) and that of twin B was within zone 2 (moderate anemia). Thus, non-invasive Doppler measurement of MCA-PSV could be an alternative to invasive amniocentesis in the management of alloimmunized twin pregnancies.

For the detection of moderate to severe fetal anemia, positive predictive values of MCA-PSV measurement reported in the past studies are 53-80% [2-5]. In other words, 20-47% of the fetuses with MCA-PSV>1.5 MoM were not actually anemic. The false positive might result from 1) factors other than fetal anemia that increase MCA-PSV and/or 2) measurement variability that often accompanies new methodology. Increased MCA-PSV is encountered in some of intrauterine growth restricted (IUGR) fetuses without anemia [9]. In IUGR, redistribution of the blood flow from the periphery to the brain could be manifested as increased MCA-PSV and decreased descending aorta-PSV (DAO-PSV). In contrast, fetal anemia causes elevation in velocities of all fetal vessels due to increased cardiac output and decreased blood viscosity. Thus, combined use of MCA-PSV and DAO-PSV can decrease the false positive rate [10]. High MCA-PSV due to measurement variability could also lead to unnecessary medical intervention. However, fetal anemia caused by alloimmunization is usually a chronic progressive disease that should induce continuous increase in MCA-PSV. In the present case, we encountered sharp increase in MCA-PSV of both twins at 31 weeks' gestation. Daily assessment of MCA-PSV revealed that increase of MCA-PSV in twin A was temporary. In contrast, there was consistent increase in the MCA-PSV of twin B, who proved to be actually anemic. Thus, when abnormally increased MCA-PSV is observed, daily measurement and/or combined measurement of DAO-PSV may be helpful to rule out false positive and to minimize unnecessary medical intervention.

In conclusion, we presented here a case of Rh (E)-incompatible dizygotic twin pregnancy. Since her previous child was affected, serial maternal titer assessment was considered to be inadequate for the surveillance of fetal anemia. In such cases,

monitoring of MCA-PSV could be a useful alternative to reduce the requirement of invasive amniocentesis that is relatively difficult in multiple pregnancies.

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Figure legends

Figure 1. Serial changes in middle cerebral artery-peak systolic velocity (MCA-PSV) for twin A and twin B

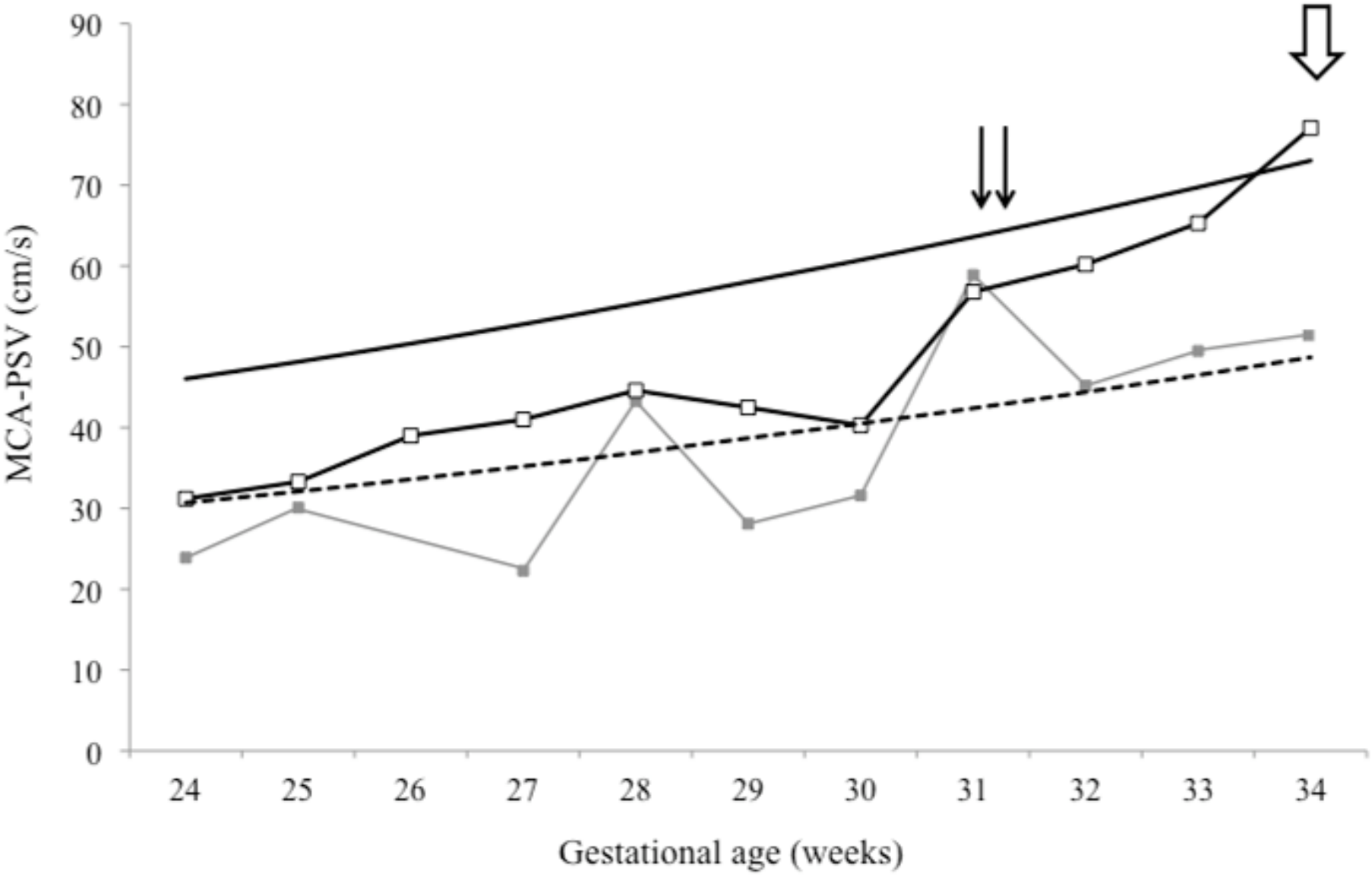
MCA-PSV values at each gestational week for twin A (closed square) and twin B (open square) are plotted on a Mari's chart [2]. The dotted line indicates the median MCA-PSV in normal pregnancies, and the solid line 1.5 multiples of the median. The solid arrows indicate timing of maternal betamethasone injections. The open arrow indicates the timing of cesarean delivery.

Tables

Table 1. Laboratory data (Blood samples taken at 30 minutes after birth)

	Twin A	Twin B
White Blood Cell ($x10^9$/L)	10.8	10.1
Hemoglobin (g/dl)	14.7	9.7
Hematocrit (%)	46.5	30.3
Platelet ($x10^9$/L)	312	299
Toatal Protein (g/dl)	4.6	5.0
Albumin (g/dl)	3.0	3.4
Total Bilirubin (mg/dl)	1.6	3.7
Direct Coombs' test	(-)	(+)

Figure 1


90
80
70
60
50
40
30
20
10
0
MCA-PSV (cm/s)
24
25
26
27
28
29
30
31
32
33
34
Gestational age (weeks)